Diagnosis and management of diabetes mellitus in cats (Part II)

Reusch, Claudia E

Diagnosis and management of diabetes mellitus in cats (Part II)

Claudia E. Reusch
Prof. Dr., Dipl ECVIM-CA
Clinic for Small Animal Internal Medicine
Vetsuisse Faculty, University of Zurich
Winterthurerstrasse 260
CH-8057 Zurich

Recurrence or persistence of clinical signs is a frequent problem and certainly the most common reason for referral of a diabetic cat. The first step is to confirm that the cat is indeed poorly regulated, i.e. has clinical signs of diabetes. High blood glucose levels may be incorrectly interpreted to be the result of poor glycemic control when in fact they are stress induced. Fructosamine concentration is also not always a reliable parameter and is sometimes moderately to markedly increased, although the cat is clinically well. A stepwise approach is helpful to define the reason for the problem.[1,2]

1. Technical problems

Errors in handling and injecting insulin are frequent and include incorrect mixing, diluting, freezing or heating of insulin, use of outdated insulin, drawing up air, inappropriate insulin dose and timing, poor injection technique and use of the wrong size of syringe (U-40/ml vs. U-100/ml; frequent error!). Careful history taking and watching the owner during the procedure will unravel the problem.

2. Insulin underdose

Most cats are well controlled with insulin doses $\leq$ 1U /kg BID. If the insulin dose is considerably less than 1 U/kg BID and underdose is a potential reason for poor glycemic control, then a stepwise increase up to 1 U/kg BID is recommended. We usually increase in steps of 0.5 U/cat BID approximately every 5 days.

3. Rule out insulin overdose and the Somogyi effect

The Somogyi effect is defined as rebound hyperglycemia due to hypersecretion of counter-regulatory hormones (mainly epinephrine, glucagon) during hypoglycemia. The latter in turn is induced by a (slight) overdose of insulin. Owners may report that days of good glycemic control are followed by several days of poor control, which should always raise the suspicion of the Somogyi effect. Diagnosis requires the documentation of hypoglycemia or a very rapid drop in blood glucose concentration followed by hyperglycemia (blood glucose usually > 17 mmol/l, 300 mg/dl) within a 12-hour period. To identify the problem, a series of BGCs may be needed, which may be best performed by home-monitoring.

4. Rule out short duration of insulin effect

Short duration is particularly common when NPH insulins are used and also occurs in some cats treated with Lente-type insulin (Caninsulin®). As a result pronounced hyperglycemia (> 15 mmol/l, 270 mg/dl) is present for several hours throughout the day. Diagnosis requires generation of BGCs, single glucose measurements (e.g. measurement only once in the morning) may lead to the erroneous assumption of insulin underdose.

5. Prolonged duration of insulin effect

Problems with prolonged duration of insulin effect are usually not seen with NPH or Lente-type insulin. It may, however, occur in some cats treated with twice daily application of PZI or Insulin Glargine. If duration of effect is longer than 12 hours, an overlap in insulin action results, which eventually leads to the Somogyi effect or to overt hypoglycemia. Indications for a prolonged duration of effect are a glucose nadir occurring 10 or more hours after insulin administration and constantly decreasing glucose concentrations beyond the time of the next insulin administration.

6. Impaired absorption of insulin

Slow absorption was a frequent problem with Ultralente insulin, which is no longer available. This problem is not considered to be important in the classes of insulins currently used.

7. Binding of insulin by insulin antibodies

Because the amino acid sequence of feline insulin differs to a varying extent from human, porcine and bovine insulin, it is logical to assume that treatment will result in the production of anti-insulin antibodies. The relevance of anti-insulin antibodies in the management of diabetic cats has not been extensively investigated. Two studies identified antibodies in 14% and 37% of cats treated with recombinant human, beef and beef/pork insulins. There was no correlation between glycemic control and the presence or absence of antibodies.[3,4] Those findings allow the assumption that problems in regulating diabetic cats are only rarely (if at all) due to anti-insulin antibodies.

8. Concurrent disorders causing insulin resistance

No insulin dose clearly defines insulin resistance. It has been suggested that insulin resistance should be suspected when glycemic control is poor despite insulin doses of > 1.5 U/kg BID, high doses (> 1.5 U/kg) are required to maintain blood glucose < 17 mmol/l (300 mg/dl) and when glycemic control is erratic and the insulin dose must be constantly adjusted.[5] Any inflammatory, infectious, neoplastic and endocrine disorder can cause insulin resistance, as well as obesity and drugs such as glucocorticoids and progestagens. In cats, insulin resistance is most commonly caused by severe obesity, chronic renal failure, chronic pancreatitis, stomatitis/oral infections, hypercortisolism and hypersomatotropism (acromegaly). The latter two diseases have the potential of causing the most severe insulin resistance. Hypercortisolism is considered to be rare: 75 – 80% of cats have pituitary-dependent disease and 20 – 25% have cortisol-secreting adrenocortical tumors. In addition to pu/pd and weight loss, which are usually due to concurrent diabetes mellitus, typical clinical signs are abdominal enlargement, an unkempt seborrheic hair coat, thinning of the hair coat, failure of hair to regrow or alopecia and muscle weakness. Severe cases may have thin fragile skin that tears easily. Cats with large pituitary masses may have CNS disturbances. However, clinical signs may also be mild and hypercortisolism is often not suspected until it becomes evident that the diabetes is difficult to regulate. The dexamethasone test and the urine corticoid-to-creatinine ratio are the preferred screening tests. Hypersomatotropism in cats is caused by a growth hormone (GH)-producing tumor in the pars distalis of the pituitary gland. GH has catabolic and anabolic effects; the latter are in part mediated by insulin-like growth factor-1. The catabolic effects are mainly due to insulin antagonism and are the reason for the diabetes mellitus. The anabolic effects include proliferation of bone, cartilage, soft tissue and organs resulting in a large body size, broad head and large paws, weight gain, prognathia inferior, respiratory difficulties because of thickening of pharyngeal tissues, degenerative arthopathy and organomegaly with potential organ dysfunction. Acromegaly has long been considered a rare disorder. However, it was recently suggested that acromegaly occurs more frequently than previously thought and is most likely underdiagnosed.[6] Since the availability of a validated GH assay for cats is a problem, diagnosis is usually based on the finding of high IGF-1 concentration. Two important points should be kept in mind. First, circulating IGF-1 is bound to proteins, which must be removed before measurement. However, not all methods are equally effective, and intra-assay inference of binding proteins may lead to false high IGF-1 levels. Therefore, only assays validated for the cat should be used. Second, IGF-1 concentrations are often low in newly diagnosed diabetic cats and increase markedly after initiating insulin therapy. Low IGF-1 levels have also been seen initially in untreated diabetic cats with acromegaly. This observation is explained by the fact that relatively high insulin concentrations are required in the portal vein for the expression and function of GH receptors on hepatocytes, and this mechanism is impaired in insulin-deficient states.[2,7]
In the majority of poorly regulated diabeteic cats it is possible to define the underlying problem by a careful work-up.

References

1. Reusch CE, Robben JH, Kooistra HS: Endocrine pancreas. In: Rijnberk A, Kooistra HS (eds.): Clinical Endocrinology of Dogs and Cats, 2nd ed., Hannover, Schlütersche Verlagsgesellschaft, 2010; 155-185.
2. Reusch CE: Feline diabetes mellitus. In: Ettinger SJ, Feldman EC (eds.): Textbook of Veterinary Internal Medicine, 7th ed., St. Louis, Missouri, Elsevier, 2010; 1796-1816.
3. Harb-Hauser M, Nelson R, Gershwin L, Neal L: Prevalence of insulin antibodies in diabetic cats. *J Vet Intern Med* (abstract) 1998; 12:245.
4. Hoenig M, Reusch C, Peterson ME: Beta cell and insulin antibodies in treated and untreated diabetic cats. *Vet Immunol Immunopathol* 2000; 77(1-2):93-102.
5. Feldman EC, Nelson RW: Feline diabetes mellitus. In: Feldman EC, Nelson RW (eds.): Canine and Feline Endocrinology and Reproduction, 3rd ed., St. Louis, Missouri, Saunders, 2004; 539-579.
6. Niessen SJ, Petrie G, Gaudiano F, Khalid M, Smyth JB, Mahoney P, Church DB: Feline acromegaly: an underdiagnosed endocrinopathy? *J Vet Intern Med* 2007; 21(5):899-905.
7. Reusch CE, Kley S, Casella M, Nelson RW, Mol J, Zapf J: Measurements of growth hormone and insulin-like growth factor 1 in cats with diabetes mellitus. *Vet Rec* 2006; 158(6):195-200.